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ORIGINAL PAPER

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Abstract *Background* Atypical depression (AD) exhibits distinct patterns of gender, bipolar-II disorder, genetic, and neuro-biological measures. Using prospective data from a community sample, this paper identifies criteria (and correlates) for an AD syndrome that maximizes the association with female sex and bipolar-II. *Methods* The Zurich cohort study is composed of 591 subjects selected from a population-based cohort of young adults in the canton of Zurich in Switzerland, screened in 1978 and followed with six interviews through 1999. Seven definitions of atypical depression were tested, using varying combinations of vegetative symptoms and mood reactivity. *Results* The atypical definitions using 2 of 3 (fatigue, overeating, oversleeping) or 2 of 2 (overeating, oversleeping) vegetative symptoms showed the strongest association with gender, bipolarity, and family history of mania. The 2/3 definition was chosen for further analysis due to its high sensitivity for identifying these characteristics. This syndrome had cumulated weighted prevalence of 16.4 % (males 9.7 %, females 23 %); when associated with major depressive episodes, 8.2 % (males 3.2 %, females 15.1 %). AD patients were characterized by high treatment rates, severity, and work impairment, early age of onset and long illness. AD was comorbid with social phobia, binge eating, neurasthenia, migraine headache, and subjective cognitive impairment.

Key words atypical depression · bipolar-II disorder · sex · prevalence

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Introduction

The concept of atypical depression (AD) is of great interest because of its association with female sex and bipolar-II disorder. AD has been found to explain, to a major extent, the gender difference in depression (Angst 2002) and to be a special depressive syndrome from a genetic point of view (Sullivan et al. 2002; Kendler et al. 1996; Stewart et al. 1993). Recently, results from a large multicentre sib-pairs study gave further support to the existence of a separate atypical dimension (Korszun et al. 2004); in a factor analysis of the familiality of symptom dimensions in depression, typical and reversed neurovegetative symptoms loaded on one factor, but gain of appetite and hypersomnia loaded negatively. A number of neuro-biological studies found differences between atypical and other forms of depression (Fotiou et al. 2003; Bruder et al. 2002, 1989; Geracioti et al. 1997; McGinn et al. 1996; Asnis et al. 1995; Quitkin et al. 1985; Harrison et al. 1984).

In previous studies, women were reported to suffer more often from AD than men (Benazzi 2003, 1999; Matza et al. 2003; Angst 2002; Asnis et al. 1995; Thase et al. 1991). At variance with these findings were some studies restricted to reversed vegetative symptoms (overeating, oversleeping) (Sullivan et al. 2002; Horwath et al. 1992; Levitan et al. 1997) or on major depressive patients (Perugi et al. 1998; McGinn et al. 1996).

An association of AD with bipolar-II disorders was observed in many studies (Angst et al. 2002; Benazzi 2001, 2000a, 2000b, 2000c), and Benazzi demonstrated that patients with AD were often characterized by a fam-

ily history of bipolar disorders (Benazzi 2003). Varying definitions of AD gave varying results (Posternak and Zimmermann 2002) and a few negative studies included very small bipolar samples (Robertson et al. 1996; Thase et al. 1991).

Unfortunately, great methodological difficulties burden research in this field mainly in the form of varying concepts of AD and selection of samples for studies. To our knowledge, with the exception of the Zurich cohort study, no other community studies assessed the full range of atypical and typical symptoms of depression prospectively. The Zurich study is, therefore, suitable for multiple analyses.

The DSM-IV's concept of atypical depression was created by DF Klein and his group from Columbia University in the USA on the basis of response to monoamine oxidase inhibitors (Sotsky and Simmens 1999; Stewart et al. 1997, 1993; Thase et al. 1991; Quitkin et al. 1991, 1990, 1989, 1988; Davidson et al. 1988; Liebowitz et al. 1988; Mountjoy et al. 1977; Ravaris et al. 1976; Robinson et al. 1973). The DSM-IV specifier for atypical features requires: a) the presence of mood reactivity, and b) two or more of the following four symptoms: interpersonal rejection sensitivity, leaden paralysis, significant weight gain or overeating and oversleeping. This definition has been questioned from several points of view. Many authors used a simpler definition of atypicality including only the two *neuro-vegetative symptoms* overeating and oversleeping (Benazzi 2002a; Matza et al. 2003; Sullivan et al. 2002, 1998; Levitan et al. 1997; Kendler et al. 1996). Latent class analyses supported this neurovegetative concept (Sullivan et al. 1998; Kendler et al. 1996) with the limitation that they had not included all five criterial symptoms of atypicality and that they did not analyse specifically bipolar-II disorders. Furthermore, neurovegetative symptoms were not found to predict treatment response (Davidson and Pelton 1986). Of interest is the finding of Levitan et al. (1997) based on a large cross-sectional community study, that pure reversed neuro-vegetative symptoms often co-occurred over the lifetime with typical vegetative symptoms.

Several authors raised doubts about *mood reactivity* as a mandatory symptom for the diagnosis of atypical depression (Angst et al. 2002; Benazzi 2002b; Parker et al. 2002, 2000; Nierenberg et al. 1998; Perugi et al. 1998; Rabkin et al. 1996; Thase et al. 1991). Recently, Henkel et al. (2004) found on the basis of a configuration frequency analysis of 403 primary care outpatients that mood reactivity may also occur without any other atypical symptoms and may not be an exclusive and prominent symptom of atypical depression. In our earlier paper, we suggested removing the hierarchical position of the symptom of mood reactivity (as used in the DSM-IV definition), but keeping all five symptoms in the definition of the atypical syndrome (Angst 2002).

Apart from overeating and oversleeping, *fatigue* has been stressed as an important element of AD. Himmelhoch and Thase (1989), Thase et al. (1989) and Thase (1991) used the term anergic depression including fatigue, motor retardation and reversed neuro-vegetative symptoms. Silverstein et al. (1999) proposed the concept of somatic depression characterized by fatigue, appetite and sleep disturbance including both increased and decreased appetite and sleep. In this context, one has to consider that the fatigue syndrome (neurasthenia of ICD-10) is associated with depression.

Originally, West and Dally (1959), Sargant (1960) and Hordern (1965) had mentioned *intensive lethargy* as a core symptom of AD. Leaden paralysis in the modern concept of AD was described and operationalized in a key paper by Stewart et al. (1993) as the physical sensation of being "heavy, leaden, or weighted down", having "low physical energy", and by questions such as "is it ever a physical effort to climb stairs or get out of a chair?" and "do your arms and legs sometimes feel heavy, as though they were full of lead?".

Recently, Parker et al. (2002) presented data suggesting the existence of an atypical syndrome with the core symptom of interpersonal rejection hypersensitivity, associated with panic disorder and social phobia, which goes back to the origin of the concept of AD (West and Dally 1959).

In summary, the concepts of atypical depression have varied enormously from the inclusion of five to two atypical symptoms. Among the five symptoms the diagnostic value of mood reactivity has been questioned most and rejection oversensitivity may represent more of a trait than a state (Angst et al. 2002).

This paper seeks to present additional data on AD from a prospective study of a community sample followed over 20 years, with a systematic analysis of varying definitions of the AD syndrome. The goal is the identification of a syndrome with a high correlation with female sex and bipolar-II disorder. In addition, we will analyse: 1) the longitudinal association and stability of atypical and typical vegetative symptoms extending the work of Levitan et al. (1997), 2) the suggestion of Silverstein et al. (1999) to include loss of appetite and insomnia into the vegetative symptoms, and 3) the proposal of Parker et al. (2002) to include panic disorder and social phobia into the concept of atypical depression.

Subjects and methods

The methodology of the Zurich study was described in this journal in detail in an earlier paper (Angst et al. 2002), which did not yet include the sixth wave in 1999.

Sample

The Zurich study comprises a sample of 4547 subjects (m = 2201; f = 2346) representative of the canton of Zurich in Switzerland, who were screened in 1978 with the Symptom Checklist 90-R (SCL-90-R) (Derogatis 1977). In order to increase the probability of the development of psychiatric syndromes, a sub-sample of 591 subjects (292 males, 299 females) was selected for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or more of the SCL-90) and a random sample of those with scores below the 85th per-

centile. The screening took place in 1978 when the male participants were 19 and the females 20 years of age. Six interview waves were conducted across 20 years from 1979 to 1999.

Symptoms and diagnoses

The atypical symptoms overeating, oversleeping, mood reactivity and rejection sensitivity were assessed in the depression section of the interview. *Excessive physical fatigue* was defined by the simultaneous presence of depression with all of three symptoms measured in the interview section on neurasthenia: exhaustion, somatic weakness and extreme susceptibility to physical fatigue. This definition approximates the DSM-IV symptom of leaden paralysis without including low energy and motor retardation. A typical vegetative syndrome was defined by insomnia plus loss of appetite or weight assessed in the context of the depression interview section.

Seven definitions of atypical depression (AD) were tested:

1) Three of 5 DSM-IV criterial symptoms of AD (non-hierarchical): mood reactivity, interpersonal rejection sensitivity, leaden paralysis, significant weight gain or overeating, oversleeping (Angst et al. 2002)
2) DSM-IV AD: hierarchical, giving priority to mood reactivity
3) Two of 4 DSM-IV criterial symptoms (rejection oversensitivity, excessive physical fatigue, overeating/weight gain, oversleeping)
4) Triadic AD (TAD): 2 of 3 criterial symptoms (excessive physical fatigue, overeating/weight gain, oversleeping)
5) Reversed vegetative syndrome: 2 of 2 criterial symptoms (overeating/weight gain, oversleeping)
6) Two of 3 symptoms (loss of energy/excessive physical fatigue, overeating/weight gain, oversleeping)
7) Two of 4 symptoms (loss of energy, excessive physical fatigue, overeating/weight gain, oversleeping)

The atypical symptoms in the definitions 1–7 had to co-occur with depressive symptoms in the last 12 months. All four interviews 1986–1999 (each covering the last 12 months) were taken into account for the cumulative diagnoses of AD. During these years, DSM was revised twice and the most recent definitions were used which could be met by the data collected in earlier years. The diagnostic criteria for comorbid conditions were based on DSM-III-R and DSM-IV criteria. Classification of psychiatric disorders was made by algorithms on the basis of DSM-III criteria (GAD, panic disorder), of DSM-III-R criteria [major depressive disorder, phobias, obsessive-compulsive disorder (OCD)], while DSM-IV criteria were applied to substance abuse/dependence. In order to avoid overdiagnosis of MDD, bipolar-II disorder was diagnosed by broad criteria for hypomania as described by Angst et al. (2003).

Statistics

Groups were compared by non-parametric tests (Kruskal-Wallis tests for continuous data, χ^2 tests for frequencies). Odds ratios (ORs) were obtained by binary logistic regression. When frequencies of exposure variables were very high or low (Table 4), the more robust risk difference (RD) was calculated in addition to the OR. The RD, also called absolute risk reduction, is the result of subtracting the proportion of cases in the unexposed from that in the exposed group. In multivariable logistic models, insignificant variables were removed from the model one-by-one, starting with the least significant one, until a final model was arrived at. Variables were kept in the model if their removal produced large (> 20 %) changes in the coefficient of any other variable. Given the exploratory nature of the study, we did not apply correction for multiple comparisons.

Results

Criterial symptoms of atypical depression of DSM-IV

The broadest non-hierarchical definition of an atypical depressive syndrome (Angst et al. 2002) requires the presence of at least three of the five criterial symptoms of DSM-IV. This classification includes DSM-IV atypical depression as a subset.

In Table 1, the non-hierarchical atypical syndrome among subjects with major depressive episodes (MDE) is presented with its rates and associations of the five

Table 1 Atypical depressive syndrome (3/5 symptoms) in subjects with major depressive episode

1986–1999	Atypical syndrome No 84	Atypical syndrome Yes 87	OR (95 % C.I.)	p (χ^2)
Symptoms	%	%		
Oversleeping	38.9	89.9	14.0 (6.2–31.4)	0.0001
Overeating	22.2	54.6	4.2 (2.1–8.3)	0.0001
Excessive physical fatigue	12.5	80.8	29.5 (12.5–69.6)	0.0001
Oversensitivity	15.3	85.9	33.7 (14.3–79.2)	0.0001
Mood reactivity	80.6	90.9	2.4 (0.98–5.9)	0.05
Loss of energy	89.9	97.0	2.8 (1.02–15.6)	0.04
Syndromes				
DSM-IV	0.0	83.8	n.c.	
2/2 symptoms[1)]	4.2	42.4	16.9 (5.0–57.6)	0.0001
2/3 symptoms[2)]	5.6	81.8	76.5 (24.7–236.9)	0.0001
2/4 symptoms[3)]	12.5	100.0	n.c. (small Ns)	0.0001
2/3 symptoms + loss of energy[4)]	60.7	93.1	8.7 (3.4–22.3)	0.0001
2/4 symptoms + loss of energy[5)]	64.3	97.7	23.6 (5.4–102.8)	0.0001

[1)] oversleeping, overeating
[2)] oversleeping, overeating, excessive physical fatigue
[3)] oversleeping, overeating, excessive physical fatigue, oversensitivity
[4)] oversleeping, overeating, excessive physical fatigue/loss of energy
[5)] oversleeping, overeating, excessive physical fatigue, loss of energy
n.c. non-computable

criterial symptoms cumulatively across four interviews from 1986 to 1999 (age 28 to 41). The highest ORs were present for the symptoms excessive physical fatigue and rejection oversensitivity. All syndromal definitions of atypical depression were strongly associated with the non-hierarchical atypical syndrome.

Atypicality in MDD and bipolar-II disorders

Table 2 presents the distribution of the atypical symptoms and syndromes in subjects with major depressive disorder (MDD) or bipolar-II (BP-II) disorder. Two symptoms (oversleeping and excessive physical fatigue) were or tended to be more common among BP-II than MDD. The atypical syndromes with 2/2 and 2/3 symptoms showed the strongest associations with bipolarity. The analogue definitions including loss of energy showed no significant association with BP-II disorders.

Atypicality and sex

With the exception of mood reactivity, all atypical symptoms were significantly more common among females than males. An elevated sex ratio (OR) in favour of females was found for all definitions of an atypical syndrome (Table 3).

Atypicality and family history of mania

In Table 4, the associations of the five atypical symptoms with a family history of mania are given. None of the symptoms was significantly associated with a positive family history of mania; excessive physical fatigue and rejection oversensitivity showed a mild trend ($p < 0.09$).

In contrast to these results, significant associations were found for atypical syndromes defined by 2/2 (OR = 3.0) and 2/3 atypical symptoms (OR = 3.9). The inclusion of loss of energy as a further symptom gave non-significant results.

Cumulative associations and stability of vegetative syndromes

Vegetative syndromes associated with depressive symptoms

Cumulatively across four interviews from age 28 to 41, atypical (reversed) vegetative syndrome (hypersomnia, increase of appetite or weight) was only in 14 (20 %) of 68 cases associated with the typical vegetative syndrome defined by insomnia and loss of appetite or loss of weight ($p < 0.46$).

The triadic atypical depressive syndrome (with or without major depression) was in 47 (34.8 %) of 135 cases associated with the typical vegetative syndrome ($p < 0.04$); similarly, the DSM-IV atypical depressive syndrome was in 30 (36.1 %) of 83 cases associated with the typical vegetative syndrome ($p < 0.02$).

Vegetative syndromes associated with MDE

In contrast to the previous significant findings, on the restricted diagnostic level of MDE, there were no significant associations present: triadic atypical depression

Table 2 Bipolar II vs. major depressive disorders (MDD): atypical depressive symptoms

1986–1999	MDD 88	BP II 83	OR (95 % C.I.)	p (χ^2)
Syndromes	%	%		
Oversleeping	62.5	74.7	1.8 (0.9–3.4)	0.086
Overeating	35.2	47.0	1.6 (0.9–3.0)	0.118
Excessive physical fatigue	44.3	60.2	1.9 (1.0–3.5)	0.04
Oversensitivity	54.6	57.8	1.1 (0.6–2.1)	0.67
Mood reactivity	85.2	88.0	1.3 (0.5–3.1)	0.60
Loss of energy and drive	94.3	92.8	0.8 (0.2–2.6)	0.68
Syndromes				
DSM-IV	46.6	50.6	1.2 (0.6–2.1)	0.5999
2/2 symptoms[1)]	17.1	36.1	2.8 (1.3–5.6)	0.0046
2/3 symptoms[2)]	42.1	57.8	2.4 (1.3–4.5)	0.0391
2/4 symptoms[3)]	56.8	69.9	1.8 (0.98–3.3)	0.0768
3/5 symptoms[4)]	51.1	65.1	1.8 (0.96–3.3)	0.0653
2/3 symptoms + loss of energy[5)]	75.0	79.5	1.3 (0.6–2.7)	0.4816
2/4 symptoms + loss of energy[6)]	79.5	83.1	1.3 (0.6–2.7)	0.5478

[1)] oversleeping, overeating
[2)] oversleeping, overeating, excessive physical fatigue
[3)] oversleeping, overeating, excessive physical fatigue, oversensitivity
[4)] oversleeping, overeating, excessive physical fatigue, oversensitivity, mood reactivity
[5)] oversleeping, overeating, excessive physical fatigue/loss of energy
[6)] oversleeping, overeating, excessive physical fatigue, loss of energy

Table 3 Sex and atypical depressive syndromes

1986–1999	Men 175	Women 203	OR (95% C.I.)	p (χ^2)
Symptoms	%	%		
Oversleeping	50.9	64.5	1.8 (1.2–2.7)	0.007
Overeating	26.9	40.4	1.8 (1.2–2.9)	0.006
Excessive physical fatigue	27.4	47.3	2.4 (0.5–3.7)	0.000
Oversensitivity	33.1	49.3	2.0 (1.3–3.0)	0.002
Mood reactivity	89.1	91.6	1.3 (0.7–2.7)	0.412
Loss of energy	86.7	95.6	3.3 (1.5–7.3)	0.002
Syndromes				
DSM-IV definition	29.7	46.8	2.1 (1.4–3.2)	0.0007
2/2 symptoms[1)]	12.0	26.1	2.6 (1.5–4.5)	0.0006
2/3 symptoms[2)]	24.0	45.8	2.7 (1.7–4.2)	0.0001
2/4 symptoms[3)]	37.7	56.7	2.2 (1.4–3.3)	0.0001
3/5 symptoms[4)]	35.4	51.7	2.0 (1.3–3.0)	0.0015
2/3 symptoms + loss of energy[5)]	66.2	84.0	2.7 (1.3–5.6)	0.0071
2/4 symptoms + loss of energy[6)]	72.1	86.8	2.5 (1.2–5.5)	0.0184

[1)] oversleeping, overeating
[2)] oversleeping, overeating, excessive physical fatigue
[3)] oversleeping, overeating, excessive physical fatigue, oversensitivity
[4)] oversleeping, overeating, excessive physical fatigue, oversensitivity, mood reactivity
[5)] oversleeping, overeating, excessive physical fatigue/loss of energy
[6)] oversleeping, overeating, excessive physical fatigue, loss of energy

Table 4 Family history (FH) of mania

	N	FH mania negative row %	FH mania positive row %	OR (95% C.I.) unadjusted	Risk difference	p
Symptoms						
Oversleeping	116	90.1	9.9	1.6 (0.8–3.1)	0.17	0.19
Overeating	68	89.5	10.5	1.5 (0.7–3.1)	0.10	0.26
Excessive physical fatigue	89	88.7	11.3	1.8 (0.9–3.6)	0.19	0.09
Oversensitivity	93	90.1	9.9	1.8 (0.9–3.5)	0.25	0.09
Mood reactivity	145	92.6	7.4	0.7 (0.4–1.5)	–0.10	0.37
Loss of energy and drive	157	91.1	8.9	n.c.	0.004	0.35
Syndromes						
DSM-IV	82	89.0	11.0	1.9 (0.6–6.1)	0.16	0.2443
2/2 symptoms[1)]	45	84.4	15.6	3.0 (0.99–9.1)	0.25	0.0440
2/3 symptoms[2)]	85	87.1	12.9	3.9 (1.0–14.4)	0.30	0.0323
2/4 symptoms[3)]	108	8.7	1.3	3.7 (0.8–17.1)	0.24	0.0752
3/5 symptoms[4)]	98	88.8	11.2	2.7 (0.7–10.2)	0.21	0.1204
2/3 symptoms + loss of energy[5)]	129	90.7	9.3	1.8 (0.4–8.4)	0.09	0.4521
2/4 symptoms + loss of energy[6)]	136	91.2	8.8	1.4 (0.3–6.4)	0.04	0.7004

[1)] oversleeping, overeating
[2)] oversleeping, overeating, excessive physical fatigue
[3)] oversleeping, overeating, excessive physical fatigue, oversensitivity
[4)] oversleeping, overeating, excessive physical fatigue, oversensitivity, mood reactivity
[5)] oversleeping, overeating, excessive physical fatigue/loss of energy
[6)] oversleeping, overeating, excessive physical fatigue, loss of energy
n.c. non-computable

was in 27 (35.1%) of 77 cases associated with typical vegetative syndromes ($p < 0.90$), whereas DSM-IV atypical depression was in 47 (36.5%) of 77 cases associated with typical vegetative syndromes ($p < 0.82$).

Temporal stability of vegetative syndromes

Associated with depressive symptoms atypical (N = 45) and typical (N = 61) vegetative syndromes were in only one-third of cases stable across at least two of the four interviews (31% and 34%, respectively).

Multivariable models of varying definitions of atypicality

In the next step, we analysed the associations of four definitions of atypical syndromes (selected based on the results of Tables 2 and 4) with variables often reported in the literature as being characteristic for atypical depression: sex, BP-II vs. MDD, and a positive family history for mania. These characteristics were used as dependent variables in multivariable logistic regressions. The different definitions of atypicality were included as predictor variables. Additionally, BP-II was included as a predictor in the model for sex and sex was included as a predictor in the models for BP-II and family history of mania. Table 5 shows that the only significant predictor for female sex was the 2/3 definition, while the only significant predictor for BP-II (vs. MDD) was the 2/2 definition. In the model for family history, the 2/2 and 2/3 definition remained as final predictors, but both were non-significant. Both were kept, because removing any one of them produced large changes in the coefficient of the remaining variable, indicating an interference.

Sensitivity and specificity

The 2/3 definition had higher sensitivity for identifying women (45.8 %), BP-II cases (57.8 %) and cases with a positive family history of mania (57.1 %) than the 2/2 definition (26.1, 36.1 and 39.3 %, respectively). In contrast, the 2/2 had higher specificity than the 2/3 definition (88.0, 83.0 and 81.2 % vs. 76, 58.0 and 64.6 %).

On the basis of these results, we chose the triadic atypical depression syndrome defined by the presence of two of the three symptoms oversleeping, overeating and excessive physical fatigue for further analyses. This syndrome had a cumulative weighted prevalence rate of 16.4 % (males 9.7 %, females 23 %). When associated with major depressive episodes (including BP-II and MDD), the prevalence rate was 8.2 % (males 3.2 %, females 15.1 %). Bipolar II had a weighted prevalence rate of 4.6 % of atypical depression and 6.9 % of non-atypical depression; major depressive disorder consisted of 3.6 % atypical and 9.1 % non-atypical depression (Table 8). As a consequence, 40 % of BP-II depression and 28.3 % of major depressive disorders were atypical.

Bipolar-II and major depressive disorders subclassified by triadic atypical depression

Tables 6–8 compare depressive and cognitive symptoms, clinical characteristics and comorbidity of atypical vs. non-atypical BP-II and MDD. We have to distinguish between significant differences as a consequence of BP/MDD differences and those due to atypicality.

In addition to the criterial symptoms for atypicality (increased appetite, weight gain, hypersomnia), most symptoms of depression occurred more frequently among atypical than non-atypical cases (Table 6). The most significant were loss of energy, irritability, inhibition, reduced sexual desire, self blame, hopelessness and fear of everyday tasks.

The typical vegetative symptoms of depression, insomnia and loss of appetite, were not associated with atypicality (Table 6). Of the 171 subjects with MDE, 45 manifested reversed and 61 typical vegetative syndromes. Among the 171 subjects with MDE, there was no significant association between typical and reversed vegetative symptoms (OR = 0.8 (0.4–1.6), $p < 0.46$). Of the 45 subjects (31.1 %) with major depressive episodes, 14 manifested both reversed and typical vegetative symptoms over the four interviews.

To our surprise, symptom scores of subjective cognitive impairment (poor concentration, impaired memory, distractibility) were significantly higher in atypical than non-atypical mood disorder (Table 7). The mean of the three cognitive symptoms in atypical cases was significantly higher for atypical [2.8 (s. d. = 0.52)] than for non-atypical cases [2.2 (s. d. = 0.83)] ($p < 0.0001$). The association of subjective cognitive impairment with atypical depression was independent of the definition of atypicality. For instance, the subjective cognitive impairment in subjects with DSM-IV atypical depression was higher [2.76 (s. d. = 0.83)] than in subjects with non-atypical depression [2.27 (s. d. = 0.58)] ($p < 0.0000$). In the case of reversed neuro-vegetative symptoms, the respective cognitive impairment scores were 2.81 (s. d. = 0.52) for atypical vs. 2.21 (s. d. = 0.52) ($p < 0.0000$) for non-atypical cases.

Uni- and bipolar disorders did not differ significantly in their cognitive impairment scores (2.48 vs. 2.54, $p < 0.23$).

As Table 8 shows, patients with triadic atypical syndromes were characterized by higher rates of females, earlier age of onset, higher rates of a family history for mania, longer illness, and higher treatment rates and

Table 5 Multivariable logistic regression models for the validators sex, BP-II and family history of mania: Odds Ratios and 95 % confidence intervals

Dependent variable	Predictor variables						
	Sex	Sampling	2/2 definition	2/3 definition	2/4 definition	3/5 definition	BP-II
(Female) sex	■	–	–	2.7 (1.7–4.2)	–	–	–
BP-II	–	–	2.8 (1.3–5.6)	–	–	–	■
FH + mania	–	–	2.0 (0.6–6.0)	1.6 (0.5–4.8)	–	–	

'–' Indicates variable not in final model; black cells indicate variable not included in initial model

Table 6 Symptoms of triadic atypical and other depression

	BP-II		MDD				
N	Atypical 41	Non-atypical 35	Atypical 37	Non-atypical 51	p (all)	p (atypical vs. non-atypical)	OR (95% C.I.) (atypical vs. non-atypical)
Symptoms	%	%	%	%			
Worse in the morning	60.4	37.1	54.1	31.4	0.0149	0.002	2.7 (1.4–5.1)
Cries easily	70.8	62.9	86.5	60.8	0.0539	0.032	1.6 (0.8–3.4)
Irritable	93.8	80.0	97.3	80.4	0.0262	0.002	9.5 (2.0–44.7)
Loss of appetite	66.7	57.1	54.1	60.8	0.6673	0.802	0.9 (0.5–1.8)
Increased appetite	64.6	14.3	51.4	17.7	0.0001	0.0001	8.1 (3.7–18.0)
Weight loss	47.9	17.1	37.8	47.1	0.0183	0.247	1.2 (0.6–2.3)
Weight gain	43.8	8.6	43.2	10.2	0.0001	0.0001	6.8 (2.8–16.2)
Inhibited	95.8	65.7	75.7	72.6	0.0044	0.006	2.5 (1.1–5.8)
Insomnia	66.7	57.1	78.4	60.8	0.2282	0.087	1.5 (0.8–3.0)
Hypersomnia	95.8	42.9	89.2	41.2	0.0001	0.0001	16.5 (6.4–42.7)
Loss of energy	100.0	82.9	97.3	92.2	0.0118	0.005	8.9 (1.1–73.7)
Social withdrawal	93.8	77.1	89.2	84.3	0.1551	0.047	2.5 (0.9–6.7)
Motor retardation	68.8	48.8	46.0	33.3	0.0055	0.012	2.1 (1.1–3.9)
Restless, agitated	70.8	48.6	56.8	49.0	0.1081	0.036	1.8 (0.9–3.4)
Loss of interest	97.9	88.6	94.6	84.3	0.0872	0.016	3.9 (1.0–15.1)
Reduced sexual desire	87.5	62.9	86.5	68.6	0.0135	0.001	2.6 (1.1–5.8)
Low self esteem	87.5	68.6	83.8	74.5	0.1384	0.027	1.6 (0.7–3.7)
Self blame	91.7	62.9	78.4	54.9	0.0003	0.0001	4.2 (1.9–9.1)
Hopeless	81.3	60.0	91.9	60.8	0.0016	0.0001	3.6 (1.6–8.3)
Fear of everyday tasks	68.8	28.6	48.7	27.5	0.0001	0.0001	3.1 (1.6–6.0)

Table 7 Cognitive symptoms in bipolar and unipolar triadic atypical depression

	BP-II		MDD			
N	Atypical 48	Non-atypical 35	Atypical 37	Non-atypical 51	p (all)	p (atypical vs. non-atypical)
Symptoms	%	%	%	%		
Indecisive	97.2	62.9	89.2	74.5	0.0001	0.000
Poor concentration	97.9	77.1	94.6	90.2	0.011	0.009
Impaired memory	91.7	68.6	89.2	64.7	0.002	0.000
N of cognitive symptoms					0.000	0.000
0	0.0	5.7	2.7	2.0		
1	2.1	17.1	2.7	13.7		
2	8.3	40	13.5	37.3		
3	89.6	37.1	81.1	47.1		
Mean (s.d.) N cognitive symptoms	2.9 (0.4)	2.1 (0.9)	2.7 (0.7)	2.3 (0.8)	0.0001	0.0001
SCL-90-R						
Mean (s.d.) N cognitive symptoms (1978–1999)	1.3 (0.7)	0.7 (0.5)	1.1 (0.8)	0.7 (0.6)	0.001	0.0001

severity (measured by the total number of the nine criterial symptoms for MDE and by the number of axis I diagnoses) and higher rates of work impairment. Compared to patients without TAD, the course of patients with TAD was significantly more severe in terms of % years of observation of depressive symptoms and treatment. TAD was comorbid to a significant extent with social phobia, binge eating and neurasthenia. Of special interest was the association of migraine with atypical depression, in contrast to tension headache which was not associated; tension headache was more often found among bipolar than unipolar depressive disorder (MDD). There was no association of atypicality with body mass index (BMI).

Are DSM-IV atypical symptoms associated with panic disorder and social phobia (Parker 2002)?

In order to analyse the questions of Parker et al. (2002) regarding an association of panic disorder and social phobia with the five DSM-IV symptoms of atypical de-

Table 8 Clinical characteristics and comorbidity of subtypes of mood disorders

N	Bipolar-II		MDD		p (all)	p (atypical vs. non-atypical)	OR (95% C.I.) (atypical vs. non-atypical)
	Atypical 48	Non-atypical 35	Atypical 37	Non-atypical 51			
Prevalence rate (%)	4.6	6.9	3.6	9.1	–	–	–
Men (% weighted)	2.4	7.6	0.8	7.7	–	–	–
Women (% weighted)	6.9	6.2	6.4	10.5	–	–	–
Women (%)	68.8	42.9	75.7	58.8	0.023	0.009	2.3 (1.2–4.4)
Age of onset (years) of sx	13.3 (4.6)	14.6 (5.0)	11.8 (4.9)	15.4 (5.7)	0.005	0.0008	0.9 (0.9–1.0)
Number of depressive sx (mean, s.d.)	8.2 (0.9)	7.0 (1.1)	7.9 (1.0)	7.3 (1.3)	0.055	0.0016	2.0 (1.5–2.7)
Distress (0–100) (mean, s.d.)	86.0 (14.5)	82.1 (16.5)	80.5 (17.4)	85.6 (13.1)	0.325	0.94	1.0 (0.98–1.01)
Mean (s.d.) % years suffered from depressive sx	66.7 (19.5)	54.2 (19.8)	65.7 (23.5)	47.8 (24.3)	0.0001	0.0001	1.03 (1.02–1.05)
Work impairment (%)	97.9	82.9	91.9	92.2	0.106	0.099	2.7 (0.8–8.9)
Treated (%)	83.3	60.0	64.9	49.0	0.005	0.003	2.7 (1.4–5.1)
Mean (s.d.) % years treated	19.7 (20.7)	9.6 (11.5)	12.1 (15.0)	11.0 (19.7)	0.006	0.004	
Hospitalized depression (%)	12.5	8.6	8.1	3.9	0.488	0.255	1.9 (0.6–6.0)
Suicide attempts (%)	33.3	25.7	27.0	21.6	0.621	0.280	1.5 (0.7–2.9)
FH + for mania (%)	22.9	2.9	0.0	4.4	0.0001	0.032	3.9 (1.0–14.4)
FH + for depression (%)	66.7	60.0	62.2	72.9	0.607	0.705	0.9 (0.5–1.7)
Ups and downs (%)	41.7	37.1	27.0	17.7	0.051	0.167	1.6 (0.8–3.1)
Comorbidity							
General anxiety disorder	47.9	31.4	24.3	35.3	0.139	0.592	1.2 (0.6–2.2)
Repeated panic attacks	41.7	31.4	37.8	27.5	0.468	0.133	1.6 (0.9–3.1)
Agoraphobia	20.8	11.4	16.2	7.8	0.284	0.073	2.3 (0.9–5.6)
Social phobia	31.3	14.3	35.1	13.7	0.032	0.003	3.0 (1.4–6.5)
Specific phobia	25.0	20.0	27.0	17.7	0.699	0.252	1.5 (0.7–3.2)
Obsessive-compulsive disorder	14.6	2.9	5.4	7.8	0.229	0.255	1.9 (0.6–6.0)
Obsessive-compulsive syndrome	39.6	17.1	24.3	25.5	0.128	0.112	1.7 (0.9–3.4)
Bulimia	6.3	0.0	8.1	2.0	0.243	0.052	6.5 (0.8–54.8)
Binge eating	31.3	11.4	18.9	11.8	0.050	0.017	2.7 (1.2–6.0)
BMI (mean, s.d.)	24.0 (4.3)	23.6 (3.3)	24.0 (5.6)	23.1 (3.4)	0.80	0.91	1.03 (0.97–1.11)
Neurasthenia	37.5	11.4	40.5	13.7	0.002	0.0001	4.3 (2.0–9.3)
Tobacco dependence	60.4	60.0	48.7	47.1	0.438	0.697	1.1 (0.6–2.1)
Alcohol abuse/dependence	43.8	51.4	13.5	21.6	0.001	0.661	0.9 (0.5–1.6)
Cannabis weekly	22.9	17.1	13.5	13.7	0.593	0.518	1.3 (0.6–2.9)
Sedatives weekly	12.5	5.7	10.8	7.8	0.720	0.282	1.8 (0.6–5.1)
Stimulant abuse/dependence	16.7	5.7	5.4	3.9	0.090	0.090	2.7 (0.8–9.1)
Substance abuse/dependence[1)]	56.3	60.0	27.0	31.4	0.003	0.947	1.0 (0.6–1.9)
Migraine IHS[2)]	14.9	8.6	30.6	18.4	0.099	0.213	1.7 (0.7–3.7)
Migraine broad definition	52.1	37.1	67.6	39.2	0.027	0.007	2.3 (1.2–4.2)
Tension headache	42.6	48.6	13.9	32.7	0.011	0.214	0.7 (0.4–1.3)
Mean (s.d.) number of axis I diagnoses (including tobacco abuse)	4.5 (2.2) median: 4	3.5 (1.6) median: 3	3.8 (1.9) median: 3	3.1 (1.6) median: 3	0.03	0.02	1.3 (1.1–1.5)
Mean (s.d.) number of axis I diagnoses (excluding tobacco abuse)	3.9 (2.2) median: 3	2.9 (1.4) median: 3	3.3 (1.8) median: 3	2.6 (1.3) median: 2	0.03	0.008	1.4 (1.1–1.6)

[1)] Without tobacco; [2)] International Headache Society
sx symptoms

pression, we carried out multivariable logistic regressions, using the five symptoms as dependent variables and entering sex, stratified sampling, bipolar-II disorder, panic disorder and social phobia as independent variables.

Social phobia was significantly associated with excessive physical fatigue, almost significantly ($p < 0.06$) with overeating, and not associated with mood reactivity, rejection oversensitivity and oversleeping. Panic disorder was not significantly associated with any atypical symptom.

Discussion

The analytic strategy of this paper was chosen on the basis of reports from the literature, summarized in the introduction, which demonstrated a strong association of

atypical depression with female sex and bipolar-II disorder. Tentatively, our goal was to identify a syndrome of atypical depression, derived from the five criterial symptoms of DSM-IV, which would discriminate best between the sexes and between bipolar II and major depressive disorders. As a further validator, a family history of mania was used in multivariable logistic regressions controlling for sex and stratified sampling. This strategy cannot validate a concept by treatment response to MAOI, which was a reason for the creation of the atypical concept.

The analysis of the five criterial symptoms of atypical depression (DSM-IV) confirmed that mood reactivity was an unspecific symptom of depression (Korszun et al. 2004). There was a trend to an association with the non-hierarchically defined atypical depressive syndrome (ADS) (taking into account all five symptoms), but mood reactivity was not associated with a family history of mania or with bipolar disorder. As a consequence of the latter finding and due to the hierarchical position of mood reactivity for the DSM-IV diagnosis of depression, the same is also true on the diagnostic level.

Rejection oversensitivity was strongly associated with the ADS and was, therefore, analysed as part of an atypical syndrome defined by 2 of 4 symptoms. This syndrome was associated with female sex and marginally with bipolar disorder and a family history of mania, but an even stronger association with sex and bipolarity was found for the reversed vegetative syndrome (2 of 2 symptoms) and a slightly broader definition including also excessive physical fatigue (2 of 3 symptoms = TAD).

Our community data indicate the advantages of using a triadic concept of atypical depression (TAD) defined by the presence of two of the following three symptoms: excessive physical fatigue, overeating, oversleeping. In contrast to the definition restricted to reversed vegetative symptoms, the broader concept of TAD is more sensitive without losing its validity in terms of our goal. Our definition of TAD is close to the concept of Silverstein et al. (1999) of a somatic depression with physical fatigue and two vegetative symptoms, but Silverstein et al.'s proposal to include also typical vegetative symptoms was not supported by our data. Further analyses will have to follow on the concept of somatic depression.

Loss of drive and energy are intuitively symptoms associated with fatigue and lethargy, which are elements of the symptom leaden paralysis. Tentatively, we added loss of drive or energy as a fourth symptom to the three that define TAD. The analyses showed no significant relationship with bipolar-II disorder and with a family history of mania; there was no trend to a better validity of this syndrome. The inclusion within the symptoms of excessive physical fatigue was also negative in its validity. Loss of drive and energy is probably an unspecific and characteristic symptom of depression in general, as suggested by the analysis of Korszun et al. (2004).

On the basis of the analyses on sensitivity and specificity for sex differences, we chose as most suitable the TAD definition. This is in line with the literature which shows a good agreement regarding the over-representation of atypicality among females, whereas a special correlation with bipolar disorder has been controversial, as mentioned in the introduction.

Weighted for stratified sampling, TAD was observed more often in depressed women (44 %) than men (17 %) and in bipolar-II disorder (40 %) than in major depressive disorders (28.3 %). The weighted prevalence rate of major triadic atypical depression (TAD) was 8.2 %, 4.6 % for bipolar-II and 3.6 % for MDD. The difference between atypical bipolar-II and MDD is small, but adds to the controversial findings reported in the literature.

Among the depressive symptoms associated with TAD, subjective cognitive impairment (reduced memory, concentration and decision-making) was most remarkable. The majority of subjects with major TAD (85.9 %) complained about all three cognitive symptoms, whereas this was the case in 43 % of non-atypical MDE. The high rate of reported cognitive impairment in subjects with atypical depression seems to be a new finding, independent of the definition of atypical depression and worth being clarified by proper neuropsychological testing.

Also of interest is the association of TAD with social phobia, supporting Parker et al.'s findings (2002), as well as the association with migraine but not with tension headache. Migraine was not significantly associated with major depressive episodes or bipolar-II disorder as usually described in the literature, but it was associated with AD, which is more common in women as migraine is.

The association of TAD with binge eating and neurasthenia is not surprising, because there is some conceptual overlap on the symptom level (overeating, physical fatigue).

Across four interviews from age 26 to 41, we found an instability of the vegetative symptoms; one-third of patients with reversed vegetative syndromes manifested longitudinally also a typical vegetative syndrome (loss of appetite/weight and insomnia). This is in agreement with the observations in a community sample investigated by Levitan et al. (1997), who described a subgroup manifesting longitudinally both reversed and typical vegetative symptoms.

Limitations

The results are based on a relatively small sample from the community although, if weighted for stratified sampling, it represents 2600 subjects. Type II errors cannot be excluded in cases of negative results in small cell occupations. The results certainly need confirmation by other larger studies, especially in clinical samples. Further studies will have to test whether the new definition of an atypical depressive syndrome is of greater validity and utility than other definitions. The findings on cognition need specific neuro-psychological testing.

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